1. What CISPLATIN is and what it is used for

- CISPLATIN is used in adults and children. The active ingredient is CISPLATIN.
- CISPLATIN belongs to one of a group of medicines called cytotoxics, which are used to kill cancer cells in tumours.
- CISPLATIN is used to treat a wide range of tumours, in particular, testicular, cervical, lung and bladder.
- Cancer and ovarian cancer that has the potential to spread to other parts of the body. Cisplatin can be given alone or in combination with other medicines.
2. Before you are given CISPLATIN

Do not take CISPLATIN if you:

- have ever had a reaction to CISPLATIN or other similar medicines containing platinum or to any of the other ingredients of the medicine – see Section 6 for details.

Take special care with CISPLATIN

Tell your doctor if:

- You have a disease affecting the kidneys, or have ever had a disease which affects the kidneys.
- You suffer from decreased bone marrow function (not enough blood cells are being made).
- You have or have ever had a disorder which affects your hearing.
- Previous use of CISPLATIN caused you to suffer a nervous disorder.
- You have had or are due to have any vaccination.

This will help your Doctor decide that Cisplatin is suitable for you. He may arrange for your liver to be monitored regularly during the course of your treatment.

Taking other medicines

There are some medicines that may interact with CISPLATIN. Make sure your doctor knows if you are taking any of the following:

- any one of a group of antibiotics known as aminoglycosides, cephaloridine (Also an antibiotic) or any diuretics (drugs which gets rid of excess water from the body), for example furosemide;
- any drugs potentially toxic to kidneys, for example amphotericin B;
- aspirin or NSAIDS (Non-Steroidal Anti-Inflammatory Drugs);
- antiepileptic medicines such as phenytoin;
- medicines used for treating acute arthritis (gout) such as allopurinol, probenecid or sulfinpyrazone (dosage adjustment of these drugs may be necessary);
- other anti-tumour drugs such as Bleomycin and/or Methotrexate;
- please tell you doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Do not take CISPLATIN if you are pregnant planning to become pregnant or if you are breast-feeding.

Driving and using machinery

Cisplatin may cause certain side effects, e.g. effects on your vision or nervous system that may reduce your driving skills and abilities to operate machinery, therefore caution should be taken following treatment with CISPLATIN.
3. How CISPLATIN is given to you

- CISPLATIN will be given to you by infusion into a vein (through a ‘drip’) under the direction of specialists in hospital. The powder is dissolved to make a solution. This is then added to a salt solution or to a sugar and salt solution, which is then given into the blood stream over a period of 6 to 8 hours.
- Your doctor will decide the dose suitable for you. It will be calculated based on your body surface area. The usual dose (single) is 20mg for each square metre of your body surface area every 3 to 4 weeks.
- A lower dose will be given if you suffer from kidney disease or decreased bone marrow function (not enough blood cells are being made).
- You will receive between 1 and 2 litres of fluid by infusion for 8 to 12 hours before you receive your CISPLATIN, to increase both the amount of urine you produce and how often you pass it. This is called diuresis. Enough fluid will be given to maintain diuresis during the 24 hours after receiving CISPLATIN.

4. Possible side effects

Like all medicines CISPLATIN can cause side effects but not everyone gets them.

CISPLATIN can cause allergic symptoms such as flushing, wheezing, rash and swelling of the face, decreased blood pressure and increased heart rate. Contact your doctor immediately if you get these symptoms.

CISPLATIN can affect male fertility. Please contact your doctor for more information.

Other side effects include:

- **Effects on your mouth, stomach and intestines:** Nausea (feeling sick), vomiting and loss of appetite are common with CISPLATIN treatment. Your doctor can give you other medicines called ‘anti-emetics’ to help if the nausea and vomiting is very bad. You may also have loss of taste or changes to your gums.
- **Effects on your kidneys and bladder:** CISPLATIN can damage your kidneys resulting in reduced function. Blood tests will be done by your doctor for raised blood levels of substances called urea, creatinine and uric acid to check your kidneys are working properly.
- **Effects on your liver:** Increased blood levels of substances that will show how well your liver is working.
- **Effects on your blood and lymph system:** Blood problems such as a decreased number of formed white and red blood cells and anaemia. This might make you more susceptible to infection and bleeding and usually occurs between days 6 and 26 after your treatment with CISPLATIN. Blood tests will be done by your doctor to check for any problems.
- **Effects on your ears:** Hearing problems including tinnitus (“ringing” in the ears) and some loss of hearing. The “ringing” in the ears usually disappears after a while.
- **Effects on your nervous system:** Tingling, pins and needles or loss of feeling in the arms and legs. It can also cause shaking, convulsions, seizures, and/or slurred speech.
- **Effects on eyes and vision:** Some loss of vision, blurring of vision, change in colour perception which returns when CISPLATIN treatment is stopped.
- **Effects on your nutrition and metabolism:** You may have decreased levels of the mineral magnesium and/or sodium in your blood. The drug may cause raised blood levels of uric acid. You may be given a drug called allopurinol to counteract this.
- **Effects on your heart and circulation:** You may notice that the rate that your heart beats changes. You may get low blood pressure. Cancer patients, including those receiving CISPLATIN are generally at an increased risk for thromboembolic events (blood clots), including stroke.
• **Effects on muscles and skin:** Mild hair loss, muscle aches, inflammation at the site of injection.

If you get any of the above side effects, or notice any other unusual side effects not listed in this leaflet, tell your doctor at once.

5. **How to store CISPLATIN**

- The unopened vials should be stored at room temperature protected from light.
- CISPLATIN should not be used after the expiry date printed on the box and on the vial. The pharmacist will check this when your medicine is prepared for you.

6. **Further information**

**What Cisplatin contains and contents of the pack**

CISPLATIN is a yellow-white, freeze dried cake and is available in single glass vials containing 50mg Cisplatin powder for injection.

The powder also contains sodium chloride and mannitol.

**Marketing Authorisation Holder:**
Pharmacia Limited
Ramsgate Road
Sandwich, Kent
CT13 9NJ
United Kingdom

**Manufacturer:**
Actavis Italy S.p.A
Viale Pasteur 10
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Walton Oaks
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Leaflet last updated: April 2010

Ref: CS 8_0
1. NAME OF THE MEDICINAL PRODUCT

Cisplatin 50

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cisplatin 50.0 mg

3. PHARMACEUTICAL FORM

Yellowish-white, freeze-dried cake in vials containing 50mg Cisplatin.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cisplatin has antitumour activity either as a single agent or in combination chemotherapy particularly in the treatment of testicular and metastatic ovarian tumours, also cervical tumours, lung carcinoma and bladder cancer.

4.2 Posology and method of administration

Route of administration: Intravenous infusion. Cisplatin should be dissolved in water for injections such that the reconstituted solution contains 1 mg/ml of Cisplatin. This solution should then be diluted in 2 litres of 0.9% saline or dextrose/saline solution (to which 37.5 g of mannitol may be added) and administration should be over a 6-8 hour period.

Adults and children

Single agent therapy

The usual dose regimen given as a single agent is 50 - 120 mg/m² by infusion once every 3 - 4 weeks or 15 - 20 mg/m² by infusion daily for 5 consecutive days, every 3 - 4 weeks.

Combination chemotherapy

Dosage may be adjusted if the drug is used in combination with other antitumour chemotherapy. With multiple drug treatment schedules Cisplatin is usually given in doses 20 mg/m² upwards every 3 - 4 weeks. Dosage should be reduced for patients with renal impairment or depressed bone marrow function.

Pre-treatment hydration with 1 - 2 litres of fluid infused for 8 - 12 hours prior to the Cisplatin will initiate diuresis. Adequate subsequent hydration should maintain diuresis during the 24 hours following administration. Aluminium containing equipment should not be used for administration of Cisplatin as it may interact with metal aluminium to form a black precipitate of platinum.
4.3 Contra-indications

Cisplatin is contra-indicated in patients who have previous allergic reactions to Cisplatin or other platinum compounds as anaphylactic-like reactions have been reported. Relative contra-indications are pre-existing renal impairment, hearing disorders and depressed bone marrow function which may increase toxicity.

4.4 Special warnings and precautions for use

This agent should only be administered under the direction of physicians experienced in cancer chemotherapy.

Renal function: Cisplatin produces cumulative nephrotoxicity. Renal function and serum electrolyte (magnesium, sodium, potassium and calcium) should be evaluated prior to initiating cisplatin treatment and prior to each subsequent course of therapy. To maintain urine output and reduce renal toxicity it is recommended that Cisplatin be administered as an intravenous infusion over 6-8 hours, as indicated in section 4.2 Posology and method of administration. Moreover, pre-treatment intravenous hydration with 1-2 litres of fluid over 8-12 hours followed by adequate hydration for the next 24 hours is recommended. Repeat courses of Cisplatin should not be given unless levels of serum creatinine are below 1.5 mg/100 ml (100 mmol/l) or blood urea below 55 mg/100 ml (9 mmol/l) and circulating blood elements are at an acceptable level. Special care has to be taken when cisplatin-treated patients are given concomitant therapies with other potentially nephrotoxic drugs (See also section 4.5 Interaction with other medicinal products and other forms of Interaction). In addition, adequate post-treatment hydration and urinary output should be monitored. Concomitant use of nephrotoxic drugs may seriously impair kidney function.

Bone marrow function: Peripheral blood counts should be monitored frequently in patients receiving Cisplatin. Although the haematologic toxicity is usually moderate and reversible, severe thrombocytopenia and leucopenia may occur. In patients who develop thrombocytopenia special precautions are recommended: care in performing invasive procedures; search for signs of bleeding or bruising; test of urine, stools and emesis for occult blood, avoiding aspirin and other NSAIDs. Patients who develop leucopenia should be observed carefully for signs of infection and might require antibiotic support and blood product transfusions.

Hearing function: Cisplatin may produce cumulative ototoxicity, which is more likely to occur with high-dose regimens. Audiometry should be performed prior to initiating therapy, and repeated audiograms should be performed when auditory symptoms occur or clinical hearing changes become apparent. Clinically important deterioration of auditory function may require dosage modifications or discontinuation of therapy.

CNS functions: Cisplatin is known to induce neurotoxicity; therefore, neurologic examination is warranted in patients receiving a cisplatin-containing treatment. Since neurotoxicity may result in irreversible damage, it is recommended to discontinue therapy with Cisplatin when neurologic toxic signs or symptoms become apparent. Anaphylactic-like reactions to Cisplatin have been observed. These reactions can be controlled by administration of antihistamines, adrenaline and/or glucocorticoids. Neurotoxicity secondary to Cisplatin administration has been reported and therefore neurological examinations are recommended. Cisplatin has been shown to be mutagenic. It may also have an anti-fertility effect. Other anti-neoplastic substances have been shown to be carcinogenic and this possibility should be borne in mind in long term use of Cisplatin. Liver function should also be monitored periodically.

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including cisplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving cisplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.
4.5 Interaction with other medicinal products and other forms of Interaction

Cisplatin is mostly used in combination with antineoplastic drugs having similar cytotoxic effects. In these circumstances additive toxicity is likely to occur.

**Nephrotoxic drugs:** Aminoglycoside antibiotics, when given concurrently or within 1-2 weeks after cisplatin administration, may potentiate its nephrotoxic effects. Concomitant use of other potentially nephrotoxic drugs (e.g. amphotericin B) is not recommended during Cisplatin therapy.

**Otoxic drugs:** Concurrent and/or sequential administration of ototoxic drugs such as aminoglycoside antibiotics or loop diuretics may increase the potential of Cisplatin to cause ototoxicity, especially in the presence of renal impairment.

**Renally excreted drugs:** Literature data suggest that Cisplatin may alter the renal elimination of bleomycin and methotrexate (possibly as a result of cisplatin-induced nephrotoxicity) and enhance their toxicity.

**Anticonvulsant agents:** In patients receiving Cisplatin and phenytoin, serum concentrations of the latter may be decreased, possibly as a result of decreased absorption and/or increased metabolism. In these patients, serum levels of phenytoin should be monitored and dosage adjustments made as necessary.

**Antigout agents:** Cisplatin may raise the concentration of blood uric acid. Thus, in patients concurrently receiving antigout agents such as allopurinol, colchicine, probenecid or sulfinpyrazone, dosage adjustment of these drugs may be necessary to control hyperuricemia and gout.

4.6 Pregnancy and lactation

Cisplatin has been shown to be teratogenic and embryotoxic in animals. The use of the drugs should be avoided in pregnant or nursing women if possible.

4.7 Effects on ability to drive and use machines

There are no known effects of Cisplatin on the ability to drive or operate machinery. However, the profile of undesirable effects (central nervous system and special sense) may reduce the patient’s driving skills and abilities to operate machinery.

4.8 Undesirable effects

**Nephrotoxicity:** Acute renal toxicity, which was highly frequent in the past and represented the major dose-limiting toxicity of Cisplatin, has been greatly reduced by the use of 6 to 8-hour infusions as well as by concomitant intravenous hydration and forced diuresis. Cumulative toxicity, however, remains a problem and may be severe. Renal impairment, which is associated with tubular damage, may be first noted during the second week after a dose and is manifested by an increase in serum creatinine, blood urea nitrogen, serum uric acid and/or a decrease in creatinine clearance. Renal insufficiency is generally mild to moderate and reversible at the usual doses of the drug (recovery occurring as a rule within 2-4 weeks); however, high or repeated Cisplatin doses can increase the severity and duration of renal impairment and may produce irreversible renal insufficiency (sometimes fatal). Renal failure has been reported also following intraperitoneal instillation of the drug. Cisplatin may also cause serious electrolyte disturbances, mainly represented by hypomagnesemia, hypocalcemia, and hypokalemia, and associated with renal tubular dysfunction. Hypomagnesemia and/or hypocalcemia may become symptomatic, with muscle irritability or cramps, clonus, tremor, carpopedal spasm, and/or tetany.

**Gastrointestinal toxicity:** Nausea and vomiting occur in the majority of Cisplatin-treated patients, usually starting within 1 hour of treatment and lasting up to 24 hours or longer. These side effects are only partially relieved by standard antiemetics. The severity of these systems may be reduced by dividing the total dose per cycle into smaller doses given once daily for five days.
**Haematologic toxicity:** Myelosuppression often occurs during Cisplatin therapy, but is mostly mild to moderate and reversible at the usual doses. Leucopenia is dose-related, possibly cumulative, and usually reversible. The onset of leucopenia occurs usually between days 6 and 26 and the time of recovery ranges from 21 to 45 days. Thrombocytopenia is also a dose-limiting effect of Cisplatin but is usually reversible. The onset of thrombocytopenia is usually from days 10 to 26 and the time of recovery ranges from about 28 to 45 days. The incidence of Cisplatin-induced anaemia (haemoglobin drop of 2 g/100 ml) ranges from 9% to 40%, although this is a difficult toxic effect to assess because it may have a complex aetiology in cancer patients. There have been rare reports of acute myelogenous leukemias and myelodysplastic syndromes arising in patients who have been treated with Cisplatin, mostly when given in combination with other potentially leukomogenic agents.

**Ototoxicity:** Unilateral or bilateral tinnitus, with or without hearing loss, occurs in about 10% of Cisplatin-treated patients and is usually reversible. The damage to the hearing system appears to be dose-related and cumulative, and it is reported more frequently in very young and very old patients. The overall incidence of audiogram abnormalities is 24%, but large variations exist. These abnormalities usually appear within 4 days after drug administration and consist of at least a 15 decibel loss in pure tone threshold. The audiogram abnormalities are most common in the 4000-8000 Hz frequencies.

**Neurotoxicity:** Peripheral neuropathies occur infrequently with usual doses of the drug. These are generally sensory in nature (e.g. paresthesia of the upper and lower extremities) but can also include motor difficulties, reduced reflexes and leg weakness. Autonomic neuropathy, seizures, slurred speech, loss of taste and memory loss have also been reported. These neuropathies usually appear after prolonged therapy, but have also developed after a single drug dose. Peripheral neuropathy may be irreversible in some patients; however, it has been partially or completely reversible in others following discontinuance of Cisplatin therapy.

**Hypersensitivity:** Anaphylactic and anaphylactic-like reactions, such as flushing, facial oedema, wheezing, tachycardia and hypotension, have been occasionally reported. These reactions may occur within a few minutes after intravenous administration. Antihistamine, adrenaline and/or glucocorticoids control all these reactions. Rarely, urticarial or maculopapular skin rashes have also been observed.

**Ocular toxicity:** Optic neuritis, papilloedema, and cortical blindness have been reported rarely in patients receiving Cisplatin. These events are usually reversible after drug withdrawal.

**Hepatotoxicity:** Mild and transient elevations of serum AST and ALT levels may occur infrequently.

**Other toxicities:** Other reported toxicities are: cardiovascular abnormalities (coronary artery disease, congestive heart failure, arrhythmias, postural hypotension, thrombotic microangiopathy, etc), hyponatremia / syndrome of inappropriate antidiuretic hormone (SIADH), mild alopecia, myalgia, pyrexia and gingival platinum line. Pulmonary toxicity has been reported in patients treated with Cisplatin in combination with bleomycin or 5-fluorouracil.

**Hyperuricaemia:** Hyperuricaemia occurring with Cisplatin is more pronounced with doses greater than 50 mg/m2. Allopurinol effectively reduces uric acid levels.

**Hypomagnesemia:** Asymptomatic hypomagnesemia has been documented in a certain number of patients treated with Cisplatin, symptomatic hypomagnesemia has been observed in a limited number of cases.

**Convulsions:** Seizures have also been reported with the use of this product.

**Cardiotoxicity:** Isolated cases of tachycardia and arrhythmia have been reported with Cisplatin chemotherapy.
**Thromboembolism:** Cancer patients are generally at an increased risk for thromboembolic events. Cerebrovascular accidents (e.g. haemorrhagic and ischaemic stroke, amaurosis fugax, sagittal sinus thrombosis) have been observed in patients receiving Cisplatin therapy. Local effects such as phlebitis, cellulitis and skin necrosis (following extravasation of the drug) may also occur.

Cisplatin can affect male fertility. Impairment of spermatogenesis and azoospermia have been reported. Although the impairment of spermatogenesis can be reversible, males undergoing Cisplatin treatment should be warned about the possible adverse effects on male fertility.

**4.9 Overdose**

There are no special instructions.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

ATC code: L01XA01

In vitro studies indicate that DNA is the principal target molecule of cis-platinum. The basis for the selectivity of the cis-isomer may reside in its ability to react in a specifically defined configuration with DNA. Modification of the DNA template results in the selective inhibition of DNA synthesis. The drug is cell cycle non-specific.

**5.2 Pharmacokinetic properties**

A biphasic plasma-decay pattern occurs in man after bolus administration. The initial plasma half-life in man is 25 - 49 minutes and the terminal half-life 3 - 4 days. In addition, a third excretory phase with a longer half-life may be postulated from the high plasma platinum concentration found after 21 days. During the terminal phase more than 90% of the drug is bound to plasma proteins. The urinary elimination of the drug is incomplete: the 5-day recovery of platinum in the urine being only 27 to 45%.

Studies in man measuring free platinum species have shown a mean terminal half-life of 48 minutes after bolus injection, which probably corresponds to the initial half-life (25 - 49 minutes) seen when total platinum is monitored and reflects the distribution of the drug. Urinary excretion of filterable platinum was greater after 6 hours infusion (75%) than after a 15 minute injection (40%) of the same dose of cis-platinum. Diuresis induced by high-volume hydration or mannitol infusion was associated with a reduction in the concentration of platinum excreted in the urine. The reduced concentration of platinum caused by the high urine volume may play a role in renal protection.

**5.3 Preclinical safety data**

No further preclinical safety data are available.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipient(s)**

Sodium chloride
Mannitol

**6.2 Incompatibilities**

None known.
6.3 Shelf-life

36 months.

6.4 Special precautions for storage

The unopened vials should be stored at room temperature, protected from light. The reconstituted solution must not be cooled or refrigerated, as cooling may result in precipitation. It should be kept at room temperature and protected from light, also during intravenous infusion. Any unused solution should be discarded.

Keep out of the reach and sight of children.

6.5 Nature and contents of container

Colourless glass vials (Type II) with bromobutyl rubber stoppers and aluminium snap-caps.

6.6 Instructions for use and handling

Cisplatin powder should be dissolved in sterile Water for Injections such that the reconstituted solution contains 1mg/ml of Cisplatin. The reconstituted solution should be diluted in 2 litres of 0.9% saline or a dextrose/saline solution (to which 37.5g of mannitol may be added). Personnel should be trained in good technique for reconstitution and handling. Pregnant staff should be excluded from working with Cisplatin. Care should be taken to prevent inhaling particles and exposing the skin to Cisplatin. Adequate protective clothing should be worn, such as PVC gloves, safety glasses, disposable gowns and masks. In the event of contact with eyes, wash with water or saline. If the skin comes into contact with the drug wash thoroughly with water and in both cases seek medical advice. Seek immediate medical attention if the drug is ingested or inhaled. All used materials, needles, syringes, vials and other items which have come into contact with cytotoxic drugs should be incinerated. Contaminated surfaces should be washed with copious amounts of water.

7. MARKETING AUTHORISATION HOLDER

Pharmacia Limited - Ramsgate Road - Sandwich - Kent - CT13 9NJ - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 00032/0334

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

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11. LEGAL CATEGORY

POM